Detailed Action

Election/Restrictions

Group I, claim(s) 1 and 31-54, drawn to a method for a functional treatment of small muscles selected from the group comprising urethral sphincters, anal sphincters, eyelid muscles, muscles of the fingers, and muscles of the larynx, in a mammal, the method comprising administering myoblasts obtainable by culturing said myoblasts in a cell culture medium.

Applicant's response to the Requirement for Restriction, filed on January 22, 2008 is acknowledged.

i) Applicant has elected the cell culture media component species within which myoblasts are to be cultured is serum of animal origin, as recited in claims 1(i), 32(i), 48(i) and 54(i);

ii) Applicant has elected the alternative method steps recited in claims 46 and 52.

iii) Applicant has elected the small muscle tissue to be treated by the inventive cultured myoblasts species is urethral sphincters, as recited in claims 48 and 54.

Upon further consideration of the claims, and as per the telephone conversation with Applicant's representative on January 3, 2008, the Examiner rejoins the species "a serum fraction of animal origin" with "a serum of animal origin" for examination purposes.

Newly submitted amendments to claims 1, 32 and 54 directed to an invention, specifically the inclusion of the non-elected cell culture media component species "a glucocorticoid" that is independent or distinct from the invention originally claimed for the following reasons: The cell culture media component species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. The cell culture media species do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features. Pinset et al (*of record) teach the culturing of myoblasts in a cell culture medium comprising fetal calf serum, insulin and at least one antioxidant and/or vitamin. Thus, the special technical feature of the invention, the myoblast obtained via the claimed cell culture conditions, does not contribute over the prior art. In addition, these cell culture media component combination species are not obvious variants of each other based on the current record.

Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 1(iv), 32(iv) and 54(iv) are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Amendments

Applicant's response and amendments, filed September 10, 2008, to the prior Office Action is acknowledged. Applicant has cancelled Claims 2-30, 49 and 51, withdrawn Claims 34-45, 47, 50 and 53, and amended Claims 1, 32, 37, 46-48 and 52-54.

The amendments to the claims do not comply with the Revised Amendment Practice of 37 CFR §1.121 (See OG Notice 23 September 2003). Specifically, the correct status of claims 37, 47 and 53 is (Withdrawn, Currently Amended).

§1.121 Manner of making amendments in applications.

(c) Claims. Amendments to a claim must be made by rewriting the entire claim with all changes (e.g., additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

(2) When claim text with markings is required. All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall

include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn- currently amended."

Claims 34-45, 47, 50 and 53 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1, 31-33, 46, 48, 52 and 54 are under consideration.

Priority

This application is a 371 of PCT/FR03/03691, filed December 12, 2003 and claims benefit of the prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c). Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) for the French application 02/15827 filed on December 13, 2002. A copy of the foreign patent application PCT/FR03/03691, published as WO 2004/055174 A1 on July 1, 2004 and a certified copy of French application 02/15827 are provided with the instant application.

Accordingly, the effective priority date of the instant application is granted as December 13, 2002.

The Examiner notes that English translations of the priority documents FR 02/15827 and PCT/FR03/03691 have not been filed with the instant application.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the September 10, 2008 response will be addressed to the extent that they apply to current rejection(s).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

1. **The prior rejection of Claims 1, 31-33, 46, 48-49, 52 and 54 under 35 U.S.C. 112, second paragraph, are withdrawn** in light of Applicant's amendments to the claims to clarify the recitation of the invention.

2. **The prior rejection of Claims 46 and 52 under 35 U.S.C. 112, second paragraph,** as being incomplete for omitting essential steps, **is withdrawn** in light of Applicant's amendment to the claims to recite the step of thawing the frozen myoblasts prior to the administration step.

3. **Claim 33 is rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 33 recites the limitation "said selection" in reference to claim 32. There is insufficient antecedent basis for this limitation in the claim because claim 32 has been amended to no longer recite a selection step.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Claims 1, 31-33, 46, 48, 52 and 54 stand rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the office action mailed April 10, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed September 10, 2008.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The inventive concept in the instant application is a cell culture medium composition and process to culture myoblasts capable of being used in cell and/or gene therapy products (pg 1, lines 5-8).

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification discloses means of extracting muscle progenitor or stem cells from muscle tissue (pg 15, Example 1), culturing said cells in a defined media to amplify the muscle precursor cells (pgs 16-19, Examples 2-5), functional testing of human muscle precursor cells (pg 20, Example 6), improved cell freezing techniques (pg 22, Example 8), and selection/amplification protocols of muscle progenitor cells from biopsies (pg 24, Example 9).

However, the claims lack enablement because neither the claims nor the specification disclose how to administer the myoblasts so as to achieve a clinically meaningful and therapeutic result.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The claims are drawn to methods of cell therapy, which is a complex and unpredictable art.

Skuk et al (Exp. Neurology 155:22-30, 1999) teach that while very efficient myoblast transplantation grafts may be obtained in mice, poor results were observed after myoblast transplantation in dogs, monkeys, and humans. The poor results of myoblast transplantation in large animals were attributed to different problems like the absence of migration of transplanted cells and the high rate of mortality of transplanted myoblasts. In humans, voluminous muscles not conditioned by damaging agents were injected with a number of myoblasts significantly smaller for a large muscle and the injections were performed at greater distance from each other than in mice. Considering that myoblasts do not migrate into the muscle, their only possibility under these last conditions is to be incorporated into the fibers immediately next to the sites of injection (pg 27, col. 1, ¶s 2-3).

Animal research has demonstrated that immune-specific reactions against the donor cells and hybrid muscle fibers take place some days after myoblast transplantation (pg 22, col. 2, ¶3). Two other problems were also signaled as limiting the efficacy of myoblast transplantation: the absence of migration of myoblasts into the muscular tissue and the massive mortality of grafted cells after the transplantation (pg 23, col. 1, lines 1-5). The conditions in rodent experiments were largely different from those used in clinical trials and this could also explain the difference of success of myoblast transplantation (pg 23, col. 1, ¶1). The art recognized a duality of results between rodent experiments and clinical trials as well as large animal models (pg 27, col. 1, ¶2).

Applicant's own post-filing work (Peyromaure et al, Urology 64(5): 1037-1041, 2004) teaches that:

> "The optimal number of muscle precursor cells to be injected into a recipient remains to be clarified in additional experiments (pg 1040, col. 2, ¶2). For clinical application, the critical question is to know whether muscle precursor cell transplantation in the lower urinary tract has only a bulk effect or could enhance sphincteric function. Information about functional characteristics and innervation of the implanted cells is lacking (pgs

1040-1041, joining ¶). Measurements of leak pressure is necessary to determine if true effect of implanted muscle precursor cells is better. Finally, there is no guarantee that the injected muscle precursor cells would incorporate into myofibers in elderly patients with urinary incontinence. It is possible that the elderly microenvironment is not as favorable. Clinical studies are needed to clarify this point. We acknowledge that muscle precursor cell injection into the normal striated urethral sphincter results in their incorporation in adult myofibers, as confirmed by our study. However, the possibility of myofiber regeneration and reinnervation after muscle precursor cell implantation in the urethral sphincter remains to be clarified." (pg 1041, col. 1, ¶ 1-2).

While the credentials of those of skill in the gene therapy art are impressive (M.D.s and Ph.D.s), their level of skill in actually practicing gene therapy for treatment of small muscles such as urethral sphincters is very low because they have not been successful in reducing cell therapy to practice. Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that myoblasts may be used to functionally treat an enormous genus of anatomically distinct small muscles, including urethral sphincters, in need of treatment from an enormous genus of etiologically and pathologically distinct medical conditions in a human of any age. This is because the artisan would have to essentially invent for themselves a determination of the frequency and location of the myoblasts to be implanted into the target tissue, the optimal number of myoblasts (myoblast-to-muscle volume ratio) to be transplanted, means of enhancing the survivability of the transplanted myoblasts, and means of overcoming or avoiding immune rejection of the donor myoblast cells and hybrid muscle fibers. One of skill in the art would need to rely solely upon the teachings of the specification for guidance in practicing the claimed invention because the prior art, including Applicant's post-filing art, teach that such obstacles have not been solved so as to achieve clinically and therapeutically meaningful results. However, the specification does not provide the requisite guidance for the practice of the claimed invention.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Response to Arguments

Applicant argues that the standard of enablement does not require that the optimum dosage and frequency be known in order for a patent to issue. Furthermore, "it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness.

Applicant's argument(s) has been fully considered, but is not persuasive. The claims require that the myoblasts administered to the subject in need achieve functional treatment. "In effect, by [claiming therapeutic activity, Applicants] are claiming in terms of use. It behooves them, therefore, to disclose how to use, as section 112 ordains..." *In re Gardner*, 427 F.2d 786, 166 USPQ 138 (C.C.P.A. 1970). However, in the instant case, while the specification discloses means of harvesting and culturing myoblasts, it is silent with how and where to administer the myoblasts so as to achieve a clinically meaningful and therapeutic result. The specification lacks the proper dosage of myoblasts and any working example. Furthermore, the state of the art at the time of the invention and Applicant's own post-filing work clearly demonstrate significant unpredictability to successfully achieve the functional restoration of urethral sphincters by myoblast transplantation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. **The prior rejection of Claims 1, 31-33, 48 and 54 under 35 U.S.C. 102(b)** as being anticipated by Chancellor et al (Neurourol. and Urodyn. 19:279-287, 2000) **is withdrawn** in light of Applicant's amendments to the claims limiting the scope of the invention to a human patient. Chancellor et al teach the patient is a rat.

6. **The prior rejection of Claims 46 and 52 under 35 U.S.C. 102(e)** as being anticipated by Chancellor et al (U.S. Patent 6,866,842) **is withdrawn** in light of Applicant's amendment to the claims reciting that the step of characterizing the myoblasts with cell cycle markers, a limitation that Chancellor et al does not disclose.

7. **Claims 1, 31-33, 48 and 54 stand rejected under 35 U.S.C. 102(e)** as being anticipated by Chancellor et al (U.S. Patent 6,866,842; *of record).

This rejection is maintained for reasons of record in the office action mailed April 10, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed September 10, 2008.

Chancellor et al disclosed a method treating urinary incontinence (col. 9, line 9) or enhancing urinary sphincters (col. 9, line 58), the method comprising the administration of myoblasts or muscle-derived stem cells. Primary myoblasts were harvested and extracted from muscle tissue, and cultured in cell culture media comprising animal sera (col.s 24-25, joining ¶), whereupon the myoblasts were assayed for desmin expression (col. 49, line 29-col. 50, line 18). The myoblasts were cultured *in vitro* and preserved their ability to differentiate, e.g. by expressing desmin, forming colonies of myotubes (col. 11, lines 8-10). Chancellor et al disclose that substances, e.g. bFGF, which enhance myoblast proliferation and differentiation *in vitro* may also increase muscle regeneration *in vivo* and prevent the development of scar tissue formation (col. 46, lines 20-23, lines 50-64; col. 47, Table 4). The cultured myoblasts may be frozen and stored indefinitely for possible future use (col. 59, lines 10-11).

Chancellor et al disclose the patient may be a human (col. 17, line 10).

The myoblasts obtained by the culturing method disclosed in the instant specification and as claimed are determined to be a product-by-process claim. The recitation of process limitations in claims 1, 32, 48 and 54 are not viewed as positively limiting the claimed product myoblast absent a showing that the process of making recited in the claims imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent myoblast products are obtainable by multiple routes. The myoblasts of Chancellor et al are structurally and functionally indistinguishable from the myoblasts of the instant application. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and referenced products. The method in which the myoblasts were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

In the instant claims, the claims recite "obtainable by culturing said myoblasts in a cell culture medium comprising serum of animal origin". Absent evidence to the contrary, the recitation "obtainable by...." is not considered to further limit the invention.

Thus, Chancellor et al anticipate claims 1, 31-33, 48 and 54.

Response to Arguments

Applicant argues that:

a) the current Office Action does not identify all the elements and limitations of claim 1 in the cited references. For example, the Office Action does not identify a reference for a growth medium with anti-oxidants or vitamins. For example, the culture medium also

includes at least one of insulin and a derivative of insulin, at least one compound selected from the class of antioxidants and vitamins, and a glucocorticoid; and

b) claim 1 is not a product-by-process claim. Furthermore, the myoblasts created and used in the claimed therapy method are not the same as any myoblasts of the cited references. The media supplemented with insulin and dexamethasone (which is a glucocorticoid) results in a greater number of myogenic cells than media without insulin and dexamethasone. Consequently, the combination results in an increase of the therapeutic potential of the myoblasts cultured in it. Thus, the myoblasts cultured in the claimed media possess a quality which distinguishes them from any myoblasts cultured according to the cited references.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), Applicant is respectfully reminded that the cell culture media components recited in claims 1(ii-iv), 32(ii-iv), 48(ii-vi) and 54(ii-iv) are non-elected species, and thus are not presently under examination. Chancellor et al teach a method of functionally treating urethral sphincters in a human comprising the step of administering myoblasts obtained by culturing said myoblasts in a cell culture medium comprising **serum of animal origin**—the instantly elected cell culture media component species embodiment.

With respect to b), the Examiner is aware that the claims are drawn to a method, not a product. However, the issue is whether or not the myoblasts of the prior art are structurally and functionally different than those presently claimed. It is the Examiner's position that the myoblasts of Chancellor et al are structurally and functionally indistinguishable from the myoblasts of the instant application. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and referenced products. No specific "quality" possessed by the myoblasts is disclosed. While the supplemental media component species may result in greater numbers of myoblast cells, Applicant has provided no evidence of record that said myoblasts possess increased therapeutic potential compared to equal numbers of myoblast cells cultured by other means. Furthermore, if the essential feature of the invention is the number of myoblasts to be administered to achieve the advantageous therapeutic potential, Applicant is

respectfully reminded that the instant specification fails to disclose the number of myoblasts to be administered to achieve the advantageous therapeutic potential.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. **The prior rejection of Claim 1, 31-32, 46, 48, 52 and 54 are rejected under 35 U.S.C. 103(a)** as obvious over Chancellor et al (Neurourol. and Urodyn. 19:279-287, 2000) in view of Yiou et al (BJU International 89(3):298-302, 2002), Yokoyama et al (Urology 57:826-831, 2001) and Sanberg et al (U.S. Patent 5,942,437) **is withdrawn** in light of Applicant's amendments to the claims.

9. **Claim 1, 31-32, 46, 48, 52 and 54 are rejected under 35 U.S.C. 103(a)** as obvious over Chancellor et al (U.S. Patent 6,866,842; *of record) in view of Sanberg et al (U.S. Patent 5,942,437; *of record), Wei et al (FEBS Letters 490(3):171-178, 2001) and Di Donna et al (Neurol. Sci. 21 (5 Suppl):S943-S951, 2000).

Determining the scope and contents of the prior art.

Chancellor et al disclosed a method treating urinary incontinence in a patient, wherein the patient may be a human (col. 9, line 9; col. 17, line 10) or enhancing urinary sphincters (col. 9, line 58), the method comprising the administration of myoblasts or muscle-derived stem cells. The method comprises the steps of harvesting and extracting primary myoblasts from muscle tissue, and cultured *in vitro* in cell culture media comprising animal sera (col.s 24-25, joining ¶), the steps of harvesting and separating the cells obtained from said cell extraction (col. 20, lines

23-25; col. 24, lines 14-42, 53-col. 25, line 10), the step of carrying out a functionality test on the suitability of the myoblasts for forming colonies, e.g. myofibers (col. 11, lines 8-10; col. 25, line 6), whereupon the myoblasts were assayed for desmin expression (col. 49, line 29-col. 50, line 18). Chancellor et al disclose that substances, e.g. bFGF, which enhance myoblast proliferation and differentiation *in vitro* may also increase muscle regeneration *in vivo* and prevent the development of scar tissue formation (col. 46, lines 20-23, lines 50-64; col. 47, Table 4). Chancellor et al disclose the step of freezing the myoblasts, and storing said cells indefinitely for possible future use (col. 59, lines 10-11).

Chancellor et al do not explicitly disclose the frozen cells are thawed prior to administration. However, Chancellor et al do disclose the administration of non-frozen myoblasts (Example 10), and thus those of ordinary skill in the art would recognize that a container of frozen myoblasts would be thawed prior to administration. Furthermore, Sandberg et al disclosed means of cryopreserving myoblasts, wherein the cells are thawed prior to transplantation (e.g. col. 6, lines 10-23, 29 and 51-65).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in anatomy, cell extraction from tissue, methods of cell tissue culture, propagation and storage, and cell transplantation into a host subject. Therefore, the level of ordinary skill in this art is high.

Neither Chancellor et al nor Sandberg et al disclose the method to comprise the step of performing a characterization of said myoblasts with cell cycle markers. However, at the time of the invention, Wei et al taught that cell cycle progression negatively regulates myocyte differentiation, and that cell cycle markers such as Cdk4 and other G1 cdks sequester MyoD and keep it inactive in the dividing myoblast, thereby preventing terminal differentiation, while the excess cdk4 drives growth and proliferation of said myoblasts (see for example, pg 176, Figure

1). Similarly, Di Donna et al taught that skeletal muscle satellite cells, an art-recognized myoblast useful in cell transplantation for muscle repair are typically inactive. While degenerating muscle fibers are eliminated by mechanisms involving partners of the immune system including macrophages, the satellite cells will proliferate, then switch their transcriptional program to allow the cells to differentiate and fuse to form myotubes which will restore the damaged fibers. A minority of the satellite cells will not follow this general pathway, but instead will return to quiescence to reform a pool of reserve satellite cells for future regeneration. This is a crucial step in the regeneration mechanism which results in the stability of the capacity of the muscle to regenerate at all stages of life. (pg S944, col. 2) Myoblast proliferation is a key step and one of the limiting factors in both regeneration and cell-mediated therapy.

In the instant claims, the claims recite "obtainable by culturing said myoblasts in a cell culture medium comprising serum of animal origin". Absent evidence to the contrary, the recitation "obtainable by...." is not considered to further limit the invention.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to modify the method of Chancellor et al to comprise the step of performing a characterization of said myoblasts with cell cycle markers because myoblast proliferation was an art-recognized key step and one of the limiting factors in both regeneration and cell-mediated therapy (Di Donna et al) and cell cycle markers such as Cdk4 and other G1 cdks sequester MyoD and keep it inactive in the dividing myoblast, thereby preventing terminal differentiation, while the excess cdk4 drives growth and proliferation of said myoblasts (Wei et al). At the time of the invention, those of ordinary skill in the art recognized the problem that cell cycle status affected the therapeutic efficacy of cell transplantation, and possessed the tools to detect specific cell cycle markers to assay the cell cycle status of a given cell, thereby achieving a means to solve the problem. An artisan would be motivated to perform a characterization of said myoblasts with cell cycle markers because the determination of the cell cycle status of a myoblast population would indicate the proportion of cells in the population that are proliferating rather than becoming quiescent or differentiating, wherein said status may also be an indicator of their potential success in transplantation therapy.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

10. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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